(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

534 628

(43) International Publication Date
27 May 2004 (27.05.2004)

PCT

(10) International Publication Number
WO 2004/043985 A1

(51) International Patent Classification[7]: C07H 17/08, A61K 31/7048

(21) International Application Number: PCT/HR2003/000058

(22) International Filing Date: 10 November 2003 (10.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P20020885A 11 November 2002 (11.11.2002) HR

(71) Applicant *(for all designated States except US)*: **PLIVA d.d.** [HR/HR]; Ulica grada Vukovara 49, H-10000 Zagreb (HR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KUJUNDZIC, Nedjeljko** [HR/HR]; Slavenskog 4, HR-10000 Zagreb (HR). **BUKVIC KRAJACIC, Mirjana** [HR/HR]; Tjardoviceva 28, HR-10000 Zagreb (HR). **BRAJSA, Karmen** [HR/HR]; Jablanska 42, HR-10000 Zagreb (HR).

(74) Agent: **PLIVA d.d.**; PRAVNI POSLOVI-Intelektualno vlasnistvo, Povrzenic, Nives, Ulica grada Vukovara 49, HR-10000 Zagreb (HR).

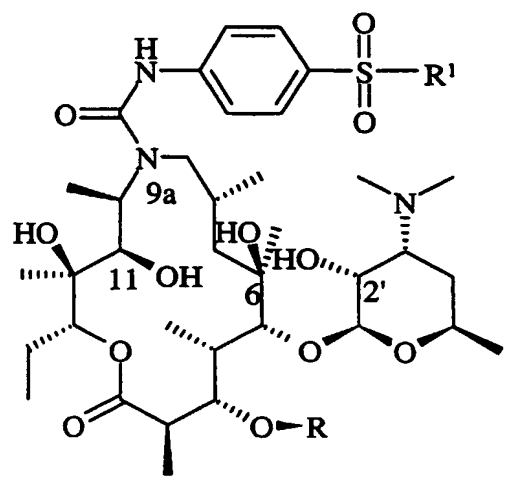
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: SUBSTITUTED 9A-N-{N'-[4-(SULFONYL)PHENYL]CARBAMOYL} DERIVATIVES OF 9-DEOXO-9-DI-HYDRO-9A-AZA-9A-HOMOERITHROMYCIN A AND 5-0-DESOSAMINYL-9-DEOXO-9-DI-HYDRO-9A-AZA-9A-HOMOERITHRONOLIDE A



(I)

(57) Abstract: The invention relates to substituted 9a-N-{N'-[4-(sulfonyl)phenyl]carbamoyl} derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-0-desosaminyl-9-deoxo-9-di-hydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series general formula (1), wherein R represents H or cladinosyl moiety and R1 represents chloro, amino, phenylamino, 2-pyridylamino, 3,4-dimethyl-4-isoxazolylamino and 5-methyl-3-isoxazolylamino group, and pharmaceutically acceptable addition salts thereof with inorganic or organic acids, to the process for their preparation of pharmaceutical composition as well as the use their compositions for sterilization rooms and medical instruments as well as for protection of wall and wooden coatings.

WO 2004/043985 A1

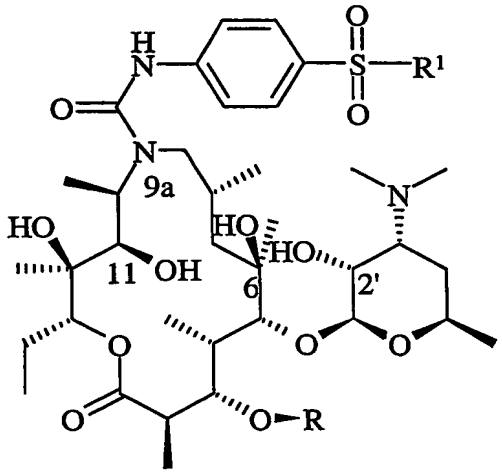
# Substituted 9a-N-{N'-[4-(sulfonyl)phenylcarbamoyl]} derivatives of 9--deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O--desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A

## Technical Field

Int. Cl. C07H17/08, A61K31/71

## Technical problem

The present invention relates to substituted 9a-N-{N'-[4-(sulfonyl)phenylcarbamoyl]} derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl--9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series having antibacterial activity of the general formula **1**




**1**

wherein R represents H or cladinosyl moiety, and $R^1$ represents chloro, amino, phenylamino, 2-pyridylamino, 3,4-dimethyl-5-isoxazolylamino and 5-methyl-3--isoxasolylamino group, to pharmaceutically acceptable addition salts there of with

inorganic or organic acids, to a process for the preparation of the pharmaceutical compositions as well as to the use of pharmaceutical compositions obtained in the treatment of bacterial infections.

**Prior Art**

Erithromycin A is a macrolide antibiotic , whose structure is characterized by 14--membered macrolactone ring having carbonyl group in C-9 position. It was found by McGuire in 1952 [*Antibiot. Chemother.*, **2** (1952) 281] and for over 50 years it has been considered as a reliable and effective antimicrobial agent in the treatment of diseases caused by Gram-positive and some Gram-negative microorganisms. However, in an acidic medium it is easily converted into anhydroerythromycin A, an inactiv C-6/C-12 metabolite of a spiroketal structure [P. Kurath et al., *Experientia* **27** (1971) 362].It is well-known that spirocyclisation of aglycone ring of erythromycin A is successfully inhibited by a chemical transformation of C-9 ketones or hydroxy groups in C-6 and/or C-12 position. By the oximation of C-9 ketones [S. Đokić et al., *Tetrahedron Lett.* **1967**: 1945] and by subsequently modifying the obtained 9(E)-oxime into 9-[O-(2--methoxyethoxy)methyloxime] erithromycin A (ROXITHROMYCIN) [G. S. Ambrieres, Fr. Pat. 2,473,525, 1981] or 9(S)-erithromycylamine [R. S. Egan et al., *J. Org. Chem.* **39** (1974) 2492] or a more complex oxazine derivative thereof, 9-deoxo-11--deoxy-9,11-{imino[2-(2-methoxyethoxyethylidene]-oxy}-9(S)-erythromycin A (DI-RITHROMYCIN) [P. Lugar i sur., *J. Crist. Mol. Struct.* **9** (1979) 329], novel semisynthetic macrolides were synthetised, whose basic characteristic, in addition to a greater stability in an acidic medium, is a better pharmacokinetics and a long half-time with regard to the parent antibiotic erythromycin A. In a third way for modifying C-9 ketones use is made of Beckmann rearrangement of 9(E)-oxime and of a reduction of the obtained imino ether (G. Kobrehel i sur., U.S. Pat. 4,328,334, 1982.) into 11-aza-10--deoxo-10-dihydroerythromycin A (9-deoxo-9a-aza-9a-homoerythromycin A) under broadening the 14-member ketolactone ring into a 15-member azalactone ring. By reductive N-methylation of 9a-amino group according to Eschweiler-Clark process (G. Kobrehel et al., BE Pat. 892,397, 1982.) or by a preliminary protection of amino group by means of conversion into the corresponding N-oxides and then by alkylation and

reduction [G. M. Bright et al., U.S. Pat., 4,474,768, 1984.] N-methyl-11-aza-10-deoxo--10-dihydroerythromycin A (9-deoxo-9a-methyl-9a-aza-9a-homoerithromycin A, AZITHROMYCIN) was synthetized, a prototype of azalide antibiotics, which, in addition to a broad antimicrobial spectrum including Gram-negative bacteria and intrcellular microorganisms, are characterized by a specific mechanism of transport to the application site, a long biological half-time and a short therapy period. In EP A 0316128 (G. M. Bright et al.) novel 9a-allyl and 9a-propargyl derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A are disclosed and in U.S. Pat. 4,492,688, 1/1985 (Bright G. M.) the synthesis and the antibactertial activity of the corresponding cyclic ethers are disclosed. In the J. Antibiotics **46** (1993) 1239 (G. Kobrehel et al.) there are further disclcsed the syntesis and the activity spectrum of novel 9-deoxo-9a-aza-11--deoxy-9a-homoerythromycin A 9a,11-cyclic carbamates and O-methyl derivatives thereof.

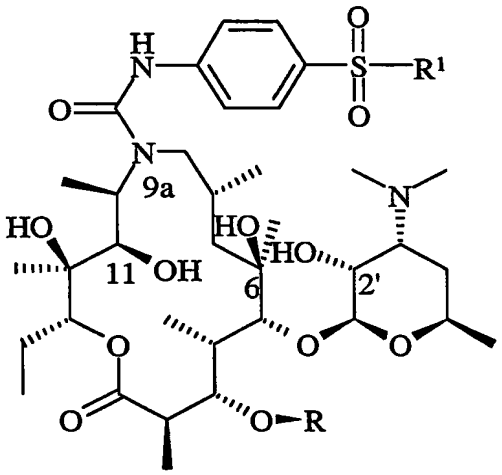
According to the known and established Prior Art, 9a-N-{N'-[4--(sulfonyl)phenylcarbamoyl]} derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A and pharmaceutically acceptable addition salts thereof with inorganic or organic acids, a process for the preparation thereof as well as the preparation methods and use a pharmaceutical preparations have not been disclosed as yet.

It has been found and it is object of the present invention that substituted 9a-N-{N'-[4-(sulfonyl)phenylcarbamoyl]} derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series and pharmaceutically acceptable addition salts thereof with inorganic or organic acids may be prepared by reacting ammonia or substituted amine with 9a-N-[N'-[4-sulfonylphenyl)carbamoyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl--9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A which are obtained by reacting of -9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9--dihydro-9a-aza-9a-homoerithronolide A with 4-(chlorosulfonyl)phenylisocyanate and optionally by reacting the obtained 9a-N-{N'-[4-(sulfonyl)phenyl]carbamoyl}

derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl--9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A with inorganic and organic acids.

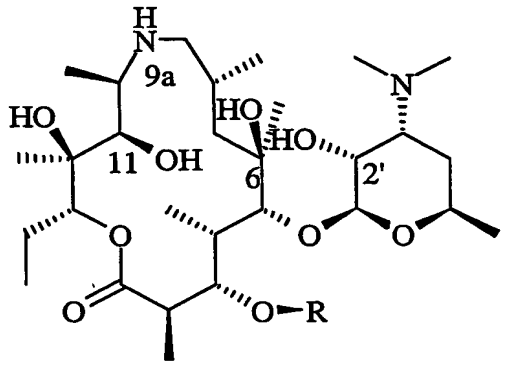
**Technical Solution**

It has been found that novel substituted 9a-N-{N'-[4-(sulfonyl)phenylcarbamoyl]} derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl--9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A of the general formula **1**, wherein R represents H or cladinosyl group and $R^1$ represents chloro group,



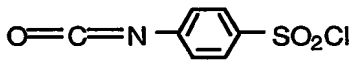

**1**

may be prepared by reacting 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5--O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A of the general formula **2**,



2

wherein R represents H or cladinosyl group, with 4-(chlorosulfonyl)phenylisocyanate formula **3**,



3

after that the compounds of general formula **1** were obtained, in which R has previous meaning, and $R^1$ represents Cl, by reaction of the compounds general formula **1** respectively, wherein R represents H or cladinosyl group and $R^1$ represents Cl, with ammonia or substituted amins general formula **4**, wherein $R^2$ represents H, phenyl group, 2-pyridyl group, 3,4-dimethyl-5-isoxazolyl group or 5-methyl-3-isoxazolyl group,

$$R^2\text{-}NH_2$$

4

in toluene, xylene or some other aprotic solvent, at a temperature of 0°C to 110°C.

Pharmaceutically acceptable acid addition salts which also represents an object of the present invention, were obtained by reaction of substituted 9a-N-{N'-[4--(sulfonyl)phenylcarbamoyl]} derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A with an at least equimolar amount of the corresponding inorganic or organic acid such as hydrochloric acid, hydroiodic acid, sulfuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, propionic acid, benzoic acid, benzene sulfonic acid, metane sulfonic

acid, lauryl sulfonic acid, stearic acid, palmitic acid, succinic acid, ethylsuccinic acid, lactobionic acid, oxalic acid, salicylic acid and similiar acids, in a solvent inert to the reaction. Addition salts are isolated by evaporating the solvent or, alternatively, by filtration after a spontaneous precipitation or a precipitation by the addition of a non-polar cosolvent.

Substituted 9a-N-{N'-[4-(sulfonyl)phenylcarbamoyl]} derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithro- nolide A of the general formula **1** and pharmaceutically acceptable addition salts with inotganic or organic acids thereof possess an antibacterial activity *in vitro*.

Minimal inhibitory concentration (MIC) is defined as the concentration which shows 90% growth inhibition, and was determinated by broth dilution methods according to National Committe for Clinical Laboratory Standards (NCCLS, M7-A2) protocols. Final concentration of test substances were in range from 64 to 0.125 μg/ml. MIC levels for all compound were determinated on panel of susceptible and resistant Gram positive bacterial strains (*S. aureus, S. pneumoniae and S. pyogenes*) and on Gram negative strains (*E. coli, H. influenzae, E. faecalis, M. catarrhalis*).

Test substances from Example 3 to 7 were active on susceptible strains of *S. pyogenes* (MIC 2 to 8 μg/ml), and on susceptible strains on *S. pneumoniae* (MIC 0.5 to 8 μg/ml). Substances from Example 3 and 4 showed showed strong antimicrobial activities on *S. pyogenes* iMLS resistante strain (MIC 2 μg/ml).

The obtained results for substances from Example 3 to 7 expressed as MIC in mg/ml suggest a potentional use thereof as sterilization agents of e.g. rooms and medical instruments and as industrial microbial agents e. g. for the protection of wall and wooden coatings.

Process for the preparation of 9a-N-{N'-[4-(sulfonyl)phenyl)carbamoyl} derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desozaminyl-9-deoxo-9--dihydro-9a-aza-9a-homoerithronolide A of this invention is illustrated by the following Examples which should in no way be construed as a limitation of the scope thereof.

**Example 1**

9-Deoxo-9-dihydro-9a-N-{[4-(chlorosulfonyl)phenyl]carbamoyl}-9a-aza-9a--homoerithromycin A

A mixture of 1.35 g (1.84 mmol) 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 0.40 (1.84 mmol) 4-(chlorosulfonyl)phenylisocyanate and 30 ml dry toluene was stirred 1 hour at the temperature 0°-5°C. The reaction mixture was evaporated at reduced pressure to dryness to give crude 9-deoxo-9-dihydro-9a-N-{[4--(chlorosulfonyl)phenyl]carbamoyl}-9a-aza-9a-homoerithromycin A. The pure product was obtained, where from by chromatography the crude product on a sillica gel column using solvent methylene chloride.

MS($ES^+$) m/z = 794.

**Example 2**

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-{[4-(chlorosulfonyl)phenyl]carbamoyl}-9a--aza-9a-homoerithronolide A

Analogously to the process disclosed in Example 1, from 1.95 g (2.0 mmol) 5-O--desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A and 0.43 g (2.0 mmol) 4-(chlorosulfonyl)phenylisocyanate in 30 ml dry toluene crude product was obtained, wherefrom by chromatography on sillica gel column using methylene chloride as a solvent. Pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-{[4-(chlorosulfonyl)phenyl]-carbamoyl}-9a-aza-9a-homoerithronolide A was obtained.

MS (ES+)m/z = 794.

**Example 3**

9-Deoxo-9-dihydro-9a-N-{[4-(aminosulfonyl)phenyl]carbamoyl}-9a-aza-9a--homoerithromycin A

The solution of 1.35 g (1.84 mmol) 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 0.4 g (1.84 mmol) 4-(chlorosulfonyl)phenyl isocyanate in 30 ml dry toluene was

stirred about 1.0 hour at the temperature 0°- 5°C. In the reaction mixture 5.0 ml (4.55 g; 61.5 mmol) 23 % water solution of ammonia was added and the reaction mixture was stirred about 30 minutes at room temperature. The crude product was filtered, wherefrom by column chromatography on sillica gel using solvent system methylen-chloride : methanol = 9 : 1. Pure 9-deoxo-9-dihydro-9a-N-{[4-(aminosulfonyl)phenyl]-carbamoyl}-9a-aza-9a-homoerithromycin A was obtained.

IR (KBr)/$cm^{-1}$ = 1727, 1638, 1593, 1552, 1126, 1013.

$^1H$ NMR (500 MHz; $CDCl_3/\delta$) = 4.41 (1H, H-1'), 4.76 (1H, H-1"), 4.00 (1H, H-3), 3.41 (1H, H-5), 3.20 (3H, 3"-$OCH_3$), 2.89 (1H, 4"), 2.50 (6H, 3'-N'$(CH_3)_2$), 2.26 (1H, H-2"a), 1.51 (1H, H-2"b), 1.29 (1H, H-8), 0.96 (3H, 10-$CH_3$), 0.89 (3H 4-$CH_3$), 0.80 (3H, H-15).

$^{13}C$ NMR (500 MHz; $CDCl_3/\delta$) = 175.6 (C-1), 155.5 (9a-NCONH), 101.9 (C-1'), 95.2 (C-1"), 84.1 (C-5), 78.3 (C-3), 48.8 (3"-$OCH_3$), 44.5 (C-2), 27.6 (C-8), 19.9 (8-$CH_3$), 9.2 (10-$CH_3$), 11.1 (C-15).

MS ($ES^+$) m/z (%) = 933.

**Example 4**

9-Deoxo-9-dihydro-9a-N-{N'-[4-(phenylaminosulfonyl)phenyl]carbamoyl}-9a-aza-9a--homoerithromycin A

Analogously to the process disclosed in Example 3, from 1,35 g (1,84 mmol) 9-deoxo--9-dihydro-9a-aza-9a-homoerithromycin A, and 0,4 g (1,84 mmol) 4--(chlorosulfonyl)phenyl isocyanate, 1,0 ml (11,0 mmol) aniline in 30 ml dry toluene 0,8 g pure 9-deoxo-9-dihydro-9a-N-{N'-[4-(aminosulfonyl)phenyl]carbamoyl}-9a-aza-9a--homoerithromycin A was obtained with following spectral data.

IR (KBr)/$cm^{-1}$ = 1727, 1638, 1593, 1552, 1126, 1013.

$^1$H NMR (500 MHz; CDCl3/δ) = 4.45 (1H, H-1'), 4.76 (1H, H-1"), 4.01 (1H, H-3), 3.38 (1H, H-5), 3.22 (3H, 3"-$OCH_3$), 2.90 (1H, 4"), 2.50 (6H, 3'-N'$(CH_3)_2$), 2.26 (1H, H-2"a), 1.52 (1H, H-2"b), 1.27 (1H, H-8), 0.90 (3H, 10-$CH_3$), 0.89 (3H 4-$CH_3$), 0.79 (3H, H-15).

$^{13}$C NMR (500 MHz; CDCl3/δ) = 179.0 (C-1), 155 (9a-NCONH), 103.8 (C-1'), 95.8 (C-1"), 84.7(C-5), 79.0 (C-3), 50.0 (3"-$OCH_3$), 46.5 (C-2), 27.9 (C-8), 20.4 (8-$CH_3$), 9.2 (10-$CH_3$), 11.3 (C-15).

MS ($ES^+$) m/z (%) = 1009.

**Example 5**

9-Deoxo-9-dihydro-9a-N-{N'-[4-(2-pyridylaminosulfonyl)phenyl]carbamoyl}-9a-aza-9a-homoerithromycin A

Analogously to the process disclosed in Example 3, from 1.35 g (1.84 mmol) 9-deoxo--9-dihydro-9a-aza-9a-homoerithromycin A, 0.4 g (1.84 mmol) 4-(chlorosulfonyl)phenyl isocyanate and 0.70 g (5.2 mmol) 2-aminopyridine in 30 ml dry toluene 0.5 g pure 9--deoxo-9-dihydro-9a-N-{N'-[4-(2-pyridylaminosulfonyl)phenyl]carbamoyl}-9a-aza-9a--homoerithromycin A was obtained with following spectral data.

IR (KBr)/$cm^{-1}$ = 1727, 1638, 1593, 1552, 1126, 1013.

$^1$H NMR (500 MHz; $CDCl_3$/δ) = 4.41 (1H, H-1'), 4.75 (1H, H-1"), 4.00 (1H, H-3), 3.38 (1H, H-5), 3.21 (3H, 3"-$OCH_3$), 2.89 (1H, 4"), 2.50 (6H, 3'-N'$(CH_3)_2$), 2.27 (1H, H-2"a), 1.48 (1H, H-2"b), 1.27 (1H, H-8), 0.89 (3H, 10-$CH_3$), 0.88 (3H 4-$CH_3$), 0.79 (3H, H-15).

$^{13}$C NMR (500 MHz; $CDCl_3$/δ) = 175.6 (C-1), 155.4 (9a-NCONH), 101.9 (C-1'), 95.1 (C-1"), 84.0 (C-5), 78.1 (C-3), 48.8 (3"-$OCH_3$), 46.5 (C-2), 27.6 (C-8), 19.9 (8-$CH_3$), 9.1 (10-$CH_3$), 11.1 (C-15).

MS ($ES^+$) m/z (%) = 1014.

**Example 6**

9-Deoxo-9-dihydro-9a-N-{N'-[4-(3,4-dimethyl-5-isoxazolylaminosulfonyl)phenyl]-carbamoyl}-9a-aza-9a-homoerithromycin A

Analogously to the process disclosed in Example 3, from 1.35 g (1.84 mmol) 9-deoxo--9-dihydro-9a-aza-9a-homoerithromycin A, 0.4 g (1.84 mmol) 4-(chlorosulfonyl)phenyl isocyanate and 0.41 g (3.67 mmol) 5-amino-3,4-dimethylisoxazole in 30 ml dry toluene 1.5 g pure 9-deoxo-9-dihydro-9a-N-{N'-[4-(3,4-dimethyl-5-isoxazolylaminosulfonyl)-phenyl]carbamoyl}-9a-aza-9a-homoerithromycin A was obtained.
MS ($ES^+$) m/z (%) =1028.

**Example 7**

9-Deoxo-9-dihydro-9a-N-{N'-[4-(5-methyl-3-isoxazolylaminosulfonyl)phenyl]-carbamoyl}-9a-aza-9a-homoerithromycin A

Analogously to the process disclosed in Example 3, from 1.35 g (1.84 mmol) 9-deoxo--9-dihydro-9a-aza-9a-homoerithromycin A, 0.4 g (1.84 mmol) 4-(chlorosulfonyl)phenyl isocyanate and 0.36 g (3.67 mmol) 3-amino-5-methylisoxazole in 30 ml dry toluene 0.40 g pure 9-deoxo-9-dihydro-9a-N-{N'-[4-(5-methyl-3-isoxazolylaminosulfonyl)-phenyl]carbamoyl}-9a-aza-9a-homoerithromycin A was obtained with following spectral data.

$^1H$ NMR (500 MHz; $CDCl_3/\delta$) = 4.42 (1H, H-1'), 4.75 (1H, H-1"), 4.01 (1H, H-3), 3.39 (1H, H-5), 3.20 (3H, 3"-$OCH_3$), 2.89 (1H, 4"), 2.50 (6H, 3'-N'$(CH_3)_2$), 2.24 (1H, H-2"a), 1.48 (1H, H-2"b), 1.28 (1H, H-8), 0.90 (3H, 10-$CH_3$), 0.87 (3H 4-$CH_3$), 0.79 (3H, H-15).

$^{13}$C NMR (500 MHz; $CDCl_3$/δ) = 175.8 (C-1), 155.6 (9a-NCONH), 101.7 (C-1'), 95.8 (C-1"), 84.0 (C-5), 78.3 (C-3), 48.9 (3"-$OCH_3$), 45 (C-2), 27.8 (C-8), 20.2 (8-$CH_3$), 9 (10-$CH_3$), 11.3 (C-15).

MS ($ES^+$) m/z (%) = 1014.

**Example 8**

5-*O*-Desosaminyl-9-deoxo-9-dihydro-9a-N-[4-(aminosulfonylphenyl)carbamoyl]-9a--aza-9a-homoerithronolide A

Analogously to the process disclosed in Example 3, from 1.15 g (2.0 mmol) 5-*O*--desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, 0.43 g (2.0 mmol) 4--(chlorosulfonyl)phenyl isocyanate and 5.0 ml (4.55 g; 61.5 mmol) 23 % water solution of ammonia in 30 ml xylene 0.60 g pure 5-*O*-desosaminyl-9-deoxo-9-dihydro-9a-N-[4--(aminosulfonylphenyl)carbamoyl]-9a-aza-9a-homoerithronolide A was obtained with following spectral data.

$^1$H NMR (500 MHz; piridin/δ) = 8.16, 7.93, 7.93, 7.5 (1H, fenilni), 5.60 (1H, H-13) 5.1 (1H, H-1'), 4.41 (1H, H-5) 4.30 (1H, H-3), 3.61 (1H, H-5'), 3.49 (1H, H-2'), 3.02 (1H, H-2), 2.61 (1H, H-3'), 2.21 (6H, 3'-$N(CH_3)_2$), 2.36 (1H, H-14a), 1.70 (1H, H-4'a), 1.87 (1H, H-14b), 1.69 (1H, H-4) 1.52 (1H, H-4'b), 1.58 (3H, 2-$CH_3$), 1.01 (3H, H-15).

$^{13}$C NMR (500 MHz; piridin/δ) =178 (C-1), 156.7 (NHCONH), 144.8, (fenil.), 133.2 (fenil.), 131.5, 129.3, 127.6, 115.3, (CH, fenil.), 103.3 (C-1'), 75.0 (C-13) 75.4 (C-3), 69.9 (C-5'), 69.2 (C-2') 68.0 (C-5), 65.4 (C-3') 45.6 (C-2), 40.3 (3'-$N(CH_3)_2$), 39.1 (C-4), 23.2 (C-14), 29.2 (C-4'), 16.7 (2-$CH_3$), 11.4 (C-15).

MS ($ES^+$) m/z (%) = 775.

**Example 9**

5-*O*-Desosaminyl-9-deoxo-9-dihydro-9a-N-{N'-[4-(phenylaminosulfonyl)phenyl]-carbamoyl}-9a-aza-9a-homoerithronolide A

Analogously to the process disclosed in Example 3, from 1.15 g (2.0 mmol) 5-*O*--desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, 0.43 g (2.0 mmol) 4--(chlorosulfonyl)phenyl isocyanate and 0.4 ml (0.419 g, 4.4 mmol) aniline in 30 ml dry toluene 0.70 g pure 5-*O*-desosaminyl-9-deoxo-9-dihydro-9a-N-{N'-[4-(phenylaminosulfonyl)phenyl]carbamoyl}-9a-aza-9a-homoerithronolide A was obtained with following spectral data.

$^1$H NMR (500 MHz; $CDCl_3/\delta$) = 4.35 (1H, H-1'), 3.86 (1H, H-3), 3.57 (1H, H-5'), 3.31 (1H, H-2'), 2.67 (1H, H-2), 2.5 (1H, H-3'), 2.30 (6H, 3'-$N(CH_3)_2$), 1.96 (1H, H-14a), 1.70 (1H, H-4'a), 1.56 (1H, H-14b), 1.30 (1H, H-4'b), 0.93 (3H, H-15).

$^{13}$C NMR (500 MHz; $CDCl_3/\delta$) =175.8 (C-1), 105.3 (C-1'), 75.4 (C-3), 69.8 (C-5'), 68.9 (C-2') 64.6 (C-3') 44.7 (C-2), 39.6 (3'-$N(CH_3)_2$), 20.9 (C-14), 29.8 (C-4'), 10.4 (C-15).

MS ($ES^+$) m/z (%) = 851.

**Example 10**

5-*O*-Desosaminyl-9-deoxo-9-dihydro-9a-N-{N'-[4-(2-pyridylaminosulfonyl)phenyl]-carbamoyl}-9a-aza-9a-homoerithronolide A

Analogously to the process disclosed in Example 3, from 1.15 g (2.0 mmol) 5-*O*--desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, 0.43 g (2.0 mmol) 4--(chlorosulfonyl)phenyl isocyanate and 0.4 g (4.2 mmol) 2-aminopyridine in 30 ml dry toluene 0.80 g pure 5-*O*-desosaminyl-9-deoxo-9-dihydro-9a-N-{N'-[4-(2-pyridylaminosulfonyl)phenyl]carbamoyl}-9a-aza-9a-homoerithronolide A was obtained with following spectral data.

$^1$H NMR (500 MHz; $CDCl_3/\delta$) = 8.30, 7.64 7.38, 7.64 (1H, aminopiridin), 4.34 (1H, H-1'), 3.84 (1H, H-3), 3.58 (1H, H-5'), 3.31 (1H, H-2'), 2.63 (1H, H-2), 2.6 (1H, H-3'), 2.29 (6H, 3'-N$(CH_3)_2$), 1.94 (1H, H-14a), 1.71 (1H, H-4'a), 1.55 (1H, H-14b), 1.29 (1H, H-4'b), 0.92 (3H, H-15).

$^{13}$C NMR (500 MHz; $CDCl_3/\delta$) = 141.5, 140.8, 114,5, 114.1 (aminopiridin), 105.4 (C-1'), 75.3 (C-3), 69.9 (C-5'), 68.9 (C-2') 64.6 (C-3') 44.7 (C-2), 39.6 (3'-N$(CH_3)_2$), 20.9 (C-14), 29.9 (C-4'), 10.4 (C-15).

MS ($ES^+$) m/z (%) = 852.

**Example 11**

5-*O*-Desosaminyl-9-deoxo-9-dihydro-9a-N-{N'-[4-(3,4-dimethyl-3--isoxazolylaminosulfonyl)phenyl]carbamoyl}-9a-aza-9a-homoerithronolide A

Analogously to the process disclosed in Example 3, from 1.15 g (2.0 mmol) 5-*O*--desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, 0.43 g (2.0 mmol) 4--(chlorosulfonyl)phenyl isocyanate and 0.45 g (4.0 mmol) 5-amino-3,4--dimethylisoxazole in 30 ml dry toluene 0.75 g pure 5-*O*-desosaminyl-9-deoxo-9--dihydro-9a-N-{N'-[4-(3,4-dimethyl-3-isoxazolylaminosulfonyl)phenyl]carbamoyl}-9a--aza-9a-homoerithronolide A was obtained with following spectral data.

MS ($ES^+$) m/z (%) = 870.

**Example 12**

5-*O*-Desosaminyl-9-deoxo-9-dihydro-9a-N-{N'-[4-(5-methyl-3--isoxazolylaminosulfonyl)phenyl]carbamoyl}-9a-aza-9a-homoerithronolide A

Analogously to the process disclosed in Example 3, from 1.15 g (2.0 mmol) 5-*O*--desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, 0.43 g (2.0 mmol) 4--(chlorosulfonyl)phenyl isocyanate and 0.39 g (4.0 mmol) 3-amino-5-methylisoxazole in 30 ml dry toluene 0.7 g pure 5-*O*-desosaminyl-9-deoxo-9-dihydro-9a-N-{N'-[4-(5-

-methyl-3-isoxazolylaminosulfonyl)phenyl]carbamoyl}-9a-aza-9a-homoerithronolide A was obtained with following spectral data.

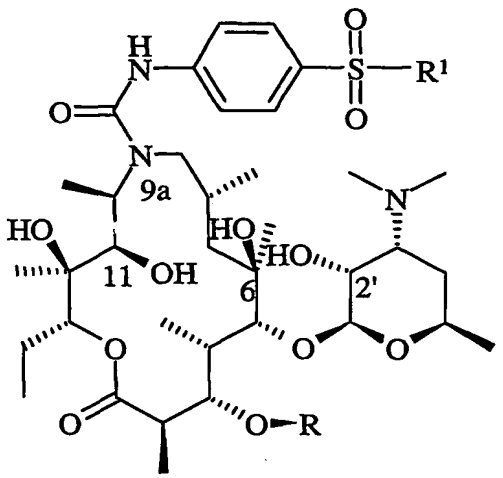
$^1$H NMR (500 MHz; $CDCl_3/\delta$) = 4.36 (1H, H-1'), 3.87 (1H, H-3), 3.56 (1H, H-5'), 3.32 (1H, H-2'), 2.65 (1H, H-2), 2.48 (1H, H-3'), 2.32 (6H, 3'-$N(CH_3)_2$), 1.95 (1H, H-14a), 1.70 (1H, H-4'a), 1.55 (1H, H-14b), 1.30 (1H, H-4'b), 0.90 (3H, H-15).

$^{13}$C NMR (500 MHz; $CDCl_3/\delta$) =105.6 (C-1'), 74.6 (C-3), 69 (C-5'), 69.3 (C-2') 64.6 (C-3') 44 (C-2), 40.1 (3'-$N(CH_3)_2$), 21.4 (C-14), 30.2 (C-4'), 10.8 (C-15).

MS ($ES^+$) m/z (%) = 856.

CLAIMS

1. Substituted 9a-N-{N'-[4-(sulfonyl)phenylcarbamoyl]} derivatives of 9-deoxo-9--dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosamynil-9-deoxo-9-dihydro--9a-aza-9a-homoerithronolide A of the general formula **1**,

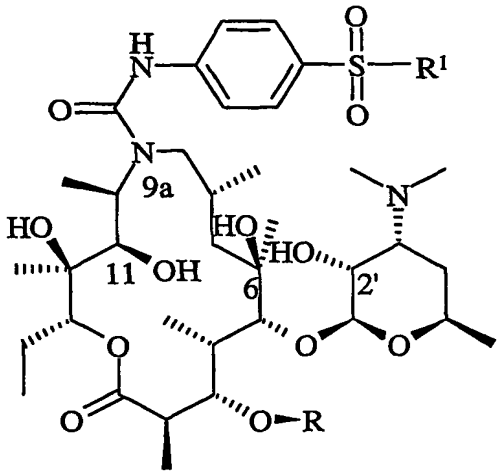


**1**

wherein R represents H or cladinosyl moiety, and $R^1$ represents chloro, amino, phenylamino, 2-pyridylamino, 3,4-dimethyl-5-isoxazolylamino and 5-methyl-3--isoxazolylamino group, and pharmacetically acceptable addition salts thereof with inorganic or organic acids.

2. A substance according to claim 1, characterized in that $R^1$ represents chloro group and R represents cladinosyl moiety.
3. A substance according to claim 1 characterized in that $R^1$ represents chloro group, and R represents H.
4. Substance according to claim 1 where $R^1$ represents amino group, and R represents cladinosyl moiety.
5. A substance according to claim 1, characterized in that $R^1$ represents phenylamino group, and R represents cladinosyl group.
6. A substance according to claim 1, characterized in that $R^1$ represents 2--pyridylamino group, and R represents cladinosyl group.

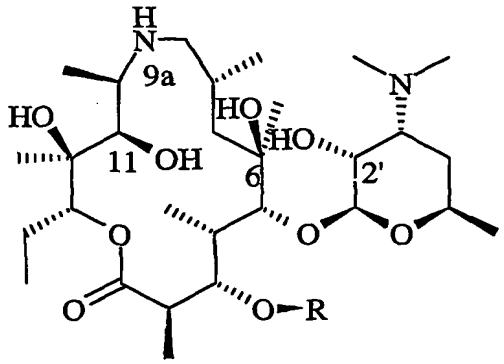
7. A substance according to claim 1, characterized in that $R^1$ represents 3,4-dimethyl--5-isoxazolyl group, and R represents cladinosyl moiety.
8. A substance according to claim 1, characterized in that $R^1$ represents 5-methyl-3--isoxazolylamino group, and R represents cladinosyl group.
9. A substance according to claim 1, characterized in that $R^1$ represents amino group and R represents H.
10. A substance according to claim 1, characterized in that $R^1$ represents phenylamino group, and R represents H.
11. A substance according to claim 1, characterized in that $R^1$ represents 2--pyridylamino group, and R represents H.
12. A substance according to claim 1, characterized in that $R^1$ represents 3,4-dimethyl--5-isoxazolylamino group, and R represents H.
13. A substance according to claim 1, characterized in that $R^1$ represents 5-methyl-3--isoxazolylamino group and R represents H.
14. A process for the preparation of substituted 9a-N-{N'-[4-(sulfonyl)phenyl carbamoyl]} derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A of the general formula **1**,




**1**

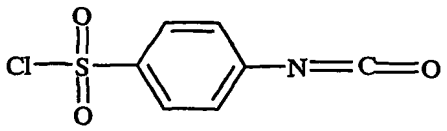
wherein $R^1$ represents chloro, amino, phenylamino, 2-pyridylamnio, 3,4-dimethyl-5--isoxazolylamino and 5-methyl-3-isoxazolylamino group and R represents H or cladinosyl group, characterized in that 9a-N-{N'-[4-(chlorosulfonyl)phenyl]-

carbamoyl} derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5--O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A general formula 1, wherein $R^1$ represents chloro group and R represent H or cladinosyl group, which can be prepared by reaction of 9-deoxo-9-dihydro-9a-aza-9a-homoerythtromicin A or 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A general formula **2**



**2**

wherein R represents H or cladinosyl group with 4-(chlorosulfonyl)phenyl isocyanate formula **3**,



**3**

are subjected to a reaction with ammonia or amine of general formula **4**,

$$R^2\text{-}NH_2$$

**4**

wherein $R^2$ represents H or phenyl, 2-pyridyl, 3,4-dimethyl-5-isoxazolyl or 5-methyl-3-isoxazolyl group, in toluene, xylene or some other aprotic solvent, at a temperature 0-110°C and then, if appropriate, to a reaction with inorganic or organic acids.

15. Pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antibacterially effective amount of the substances according to claim 1.

16. A use of a substance of according to any claims 1-13 for preparing compositions for sterilization rooms and medical instruments as well as for protection of wall and wooden coatings.

# INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 03/00058

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H17/08 A61K31/7048

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 00 66603 A (MARU & SCARON ;MUTAK STJEPAN (HR); KUJUND & ZCARON (HR); MAR & SCA) 9 November 2000 (2000-11-09) the whole document | |
| A | EP 0 657 464 A (PLIVA PHARM & CHEM WORKS) 14 June 1995 (1995-06-14) the whole document | |
| A | KUJUNDZIC, N. ET AL: "Azalides: synthesis and antibacterial activity of novel 9a-(N'-substitute carbamoyl and thiocarbamoyl) derivatives of 9-deoxo-9a-aza-9a- homoerythromycin A" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY (1995), 30(6), 455-62 , 1995, XP004040166 the whole document | |

[ ] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 24 February 2004 | 03/03/2004 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Klein, D |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
HR 03/00058

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 0066603 A | 09-11-2000 | HR 990130 A1 | 31-10-2001 |
| | | AT 244258 T | 15-07-2003 |
| | | AU 767681 B2 | 20-11-2003 |
| | | AU 4135000 A | 17-11-2000 |
| | | BG 106173 A | 31-07-2002 |
| | | BR 0010231 A | 19-02-2002 |
| | | CA 2372977 A1 | 09-11-2000 |
| | | CN 1351606 T | 29-05-2002 |
| | | CZ 20013913 A3 | 17-04-2002 |
| | | DE 60003671 D1 | 07-08-2003 |
| | | DK 1175429 T3 | 20-10-2003 |
| | | EE 200100582 A | 17-02-2003 |
| | | EP 1175429 A1 | 30-01-2002 |
| | | WO 0066603 A1 | 09-11-2000 |
| | | HU 0201146 A2 | 29-07-2002 |
| | | JP 2002543213 T | 17-12-2002 |
| | | NO 20015346 A | 01-11-2001 |
| | | NZ 515278 A | 30-06-2003 |
| | | PL 351402 A1 | 07-04-2003 |
| | | PT 1175429 T | 28-11-2003 |
| | | SI 1175429 T1 | 31-12-2003 |
| | | SK 15702001 A3 | 04-04-2002 |
| | | TR 200103143 T2 | 22-04-2002 |
| | | ZA 200108484 A | 16-01-2003 |
| EP 0657464 A | 14-06-1995 | HR 931480 A1 | 31-08-1996 |
| | | AT 144778 T | 15-11-1996 |
| | | BG 61571 B1 | 30-12-1997 |
| | | BG 99242 A | 29-09-1995 |
| | | CA 2137395 A1 | 09-06-1995 |
| | | CN 1109890 A ,B | 11-10-1995 |
| | | CZ 9403082 A3 | 12-07-1995 |
| | | DE 69400817 D1 | 05-12-1996 |
| | | DE 69400817 T2 | 22-05-1997 |
| | | EP 0657464 A1 | 14-06-1995 |
| | | ES 2096401 T3 | 01-03-1997 |
| | | HU 69283 A2 | 28-09-1995 |
| | | JP 3131546 B2 | 05-02-2001 |
| | | JP 7252292 A | 03-10-1995 |
| | | PL 306154 A1 | 12-06-1995 |
| | | RO 113854 B1 | 30-11-1998 |
| | | RU 2131878 C1 | 20-06-1999 |
| | | SI 9400434 A | 30-06-1995 |
| | | SK 146994 A3 | 11-07-1995 |
| | | US 5629296 A | 13-05-1997 |